REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration, because the amendments amplify issues previously discussed throughout prosecution; does not present any additional claims; relates to matters of form rather than substance because the added language was already present in the claims, and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented because it is made in response to arguments raised in the final rejection. Entry of the Amendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

1. Status of the Claims

Claims 1-48 are pending. Claims 14-48 are withdrawn from consideration. Claims 1-13 and 45-48 stand rejected. Applicants note that the Office Action Summary incorrectly sets forth that claims 14-48 stand withdrawn. Claims 14-44 stand withdrawn. Claims 45-48 stand pending and rejected.

Applicants have canceled withdrawn claims 14-44. Applicants have also cancelled claims 10 and 48. The cancelled claims were canceled without prejudice to or disclaimer of the subject matter contained therein. Applicants reserve the right to pursue the canceled subject matter in one or more continuations or divisional applications.

Applicants have amended claims 1-9, 11-13, and 45-47. Support for the claim amendments can be found for example in the original claims, and page 31, lines 14-16 (glycine 170 to valine and "mouse"). Accordingly, Applicants submit no prohibited new matter will be introduced by entry of the amendments to the claims.

2. Withdrawn Rejections

Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. §§ 112, first paragraph. Applicants note the Office's indication on pages 10-11 that (1) the HBM transgene exhibits changes in lipid levels is withdrawn, (2) withdrawal of the rejection regarding 15 contiguous polynucleotides, (3) rejection with regard to the recitation of "bone human cells".

3. **Double Patenting Reject**

The double patenting rejection will be held in abeyance until subject matter is found allowable that continues to be rejected under the doctrine of judicially created obviousness-type double patenting. However, Applicants submit that in view of the election in response to the restriction in USSN 10/477,238, the rejection should be withdrawn.

4. **Rejections Under 35 U.S.C. §§ 112, First Paragraph (Written Description)**

Claims 1-13, and 45-48 are newly rejected under 35 U.S.C. §§ 112, first paragraph, as allegedly lacking sufficient written description. The Office admits that the specification teaches the amino acid sequences of human LRP-5, human LRP-6, and mouse LRP-5. However, the Office asserts that homologs of SEQ ID NO: 4 are not taught.

Applicants traverse the rejection. Applicants teach that if the homologous substitution is made in the mouse sequence as ossurs in the human sequence, it would likewise be a glycine to valine substituteion. That would occur at amino acid residue 170 in the mouse sequence as opposed to residue 171 in the human sequence. As correctly noted by the Office, amino acid 171 of the mouse sequence is not a glycine, but rather a glutamic acid. The analogous substitution in the mouse gene as compared to the human sequence is discussed in the specification at least at page 34, lines 14-16. Applicants have amended the claims to more distinctly refer to the homologous substitution in the mouse sequence. The claims as amended are directed to a transgenic mouse comprising either the human or mouse sequences with the described glycine to valine substitution at the appropriate spot in those sequences respectively.

In view of the amendments to claims 1-9, 11-13, and 45-47, Applicants submit that the claims have appropriate written description as discussed in the specification. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

5. Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

The Office maintains the rejection of claims 1-13 and 45-48 in a modified form. Office Action, pages 7-10. The Office admits that the specification enables a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence encoding human HBM protein, operably linked to a promoter, stably integrated in its genome and wherein the mouse exhibits increased bone mass. Office Action, page 8. However, the Office contends that the specification does not reasonably enable a transgenic rodent comprising a nucleic acid sequence comprising SEQ ID NO: 2 or a homolog which encodes a glycine 171 to valine substitution." Office Action, page 8.

Applicants traverse the rejection to the extent it applies to the claims as amended. The current claims are directed to a "transgenic mouse" not a "transgenic rodent." Additionally, the claims more clearly recite the homolog mouse sequence with a glycine to valine substitution at residue 170. The glycine to valine substitution occurs in the mouse sequence at residue 170 and in the human homolog, at position 171. Applicants assert that based on the amino acid sequence and the tertiary structure of the wild-type LRP5, the skilled artisan would be able to readily determine equivalent glycine to valine substitutions in other species. Applicants additionally point out that in claim 48, Applicant claimed "mice or rats." Applicants submit that a transgenic rat is supported by the specification and a *prima facie* case of lack of enablement was never adduced for this claim by the Office. However, in an effort to advance the prosecution, Applicants have canceled the claim.

Thus in view of the amendments to the claims, and the above arguments, Applicants submit that the claims as amended are enabled. Accordingly, the rejection should respectfully be withdrawn, and the claims allowed.

6. Response to Applicants

On pages 10-16, the Office responds to Applicants' arguments submitted with the response dated April 27, 2006. To the extent necessary, in view of the amendments to the claims, Applicants address the Office's reply to Applicants' arguments, which appears on pages 10-16 of the Office Action.

The first argument that is maintained is whether a transgenic rodent is enabled. In an effort to advance the prosecution, Applicants have amended the claims to be directed to transgenic mice expressing the human HBM protein or mouse homolog. Accordingly, the rejection should be withdrawn. The rejection should be withdrawn as the claims are now directed to transgenic mice.

The Office then raises the issue that only some of the rejected claims (*i.e.,* Claims 2 and 46) are rejected as lacking sufficient enablement, because they do not recite a phenotype, and that absent a phenotype it is not clear how to use the claimed rodents. Office Action, page 13. Claims 2 and 46 have been amended to recite a phenotype, and accordingly obviate the rejection. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The primary and tertiary structure, especially in the areas equivalent to where amino acid residue 171 is found in the human HBM/LRP5 sequence is highly conserved. This is discussed in the specification at least at page 31, lines 14-16 and page 46, lines 24-27. Thus, identifying homologs in other species would have been enabled given what is taught in the specification, as well as what was known in the art at the time. However, as the claims have been amended to be directed to transgenic mice comprising either the mouse sequence with the G170→V substitution or the human sequence with G171→V, Applicants submit that these sequences are enabled by the disclosure and the rejection should be withdrawn.

Regarding the rejection in view of Elbrecht, Applicants maintain their traversal. Elbrecht is applied for allegedly teaching "that using episomal plasmids that do not integrate into the genome results in mosaic mice because the plasmid injected into the fertilized egg of the mice distributes randomly upon cell division. It thus follows that an artisan cannot reliably arrive at mice with a bone phenotype as there is now way to control how many copies of plasmid make its way into bone cells such that a bone phenotype is seen. As such, because Elbrecht et al. teach that making transgenic mice is unpredictable, an artisan is not enabled to arrive at the claimed invention." Office Action, pages 14-15.

Applicants have made a transgenic mouse which expresses a bone phenotype. Determination of whether insertion of the gene is stable or episomal was readily determinable. The skilled artisan would have been able to determine at the time of filing that the transgenic mouse has the integrated transgene by testing the mouse tail of the putative transgenic animal for the presence of the gene, location, and copy number. Additionally, Applicants point out that the Office's response quoted above disagrees with the enablement rejection set forth on page 8, which states that a transgenic mouse comprising a transgene construction comprising a nucleic acid sequence....stably integrated in its genome..." is enabled. Finally, in view of the amendments to the claims, the rejection is obviated as the claims now recite a mouse having somatic and germ cells comprising the specified nucleic acids.

With regard to the enablement rejection, because the claims allegedly encompass gene therapy, given that the claims have been amended to recite that both the germ cells "and" the somatic cells comprise the specified nucleic acids, gene therapy is no longer encompassed. In view of the amendment to the claims, Applicants respectfully request withdrawal of the rejection.

In view of the above arguments and amendments, Applicants submit all the previously maintained rejections have been explained and overcome. Accordingly, Applicants respectfully request withdrawal and allowance of the claims.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited. In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required or if a Notice of Appeal fee is required to maintain pendency, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,
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